```
   1 ATGGCGCCAC CACCAGCTAG AGTACATCTA GGTGCGTTCC TGGCAGTGAC TCCGAATCCC GGGAGCGCAG CGAGTGGGAC AGAGGCAGCC GCGGCCACAC
     TACCGCGGTG GTGGTCGATC TCATGTAGAT CCACGCAAGG ACCGTCACTG AGGCTTAGGG CCCTCGCGTC GCTCACCCTG TCTCCGTCGG CGCCGGTGTG
   1 MetAlaProP roProAlaAr gValHisLeu GlyAlaPheL euAlaValTh rProAsnPro GlySerAlaA laSerGlyTh rGluAlaAla AlaAlaThrPro

 101 CCAGCAAAGT GTGGGGCTCT TCCGCGGGGA GGATTGAACC ACGAGGCGGG GGCCGAGGAG CGCTCCCTAC CTCCATGGGA CAGCACGGAC CCAGTGCCCG
     GGTCGTTTCA CACCCCGAGA AGGCGCCCCT CCTAACTTGG TGCTCCGCCC CCGGCTCCTC GCGAGGGATG GAGGTACCCT GTCGTGCCTG GGTCACGGGC
  35   SerLysVa lTrpGlySer SerAlaGlyA rgIleGluPr oArgGlyGly GlyArgGlyA laLeuProTh rSerMetGly GlnHisGlyP roSerAlaArg

 201 GGCCCGGGCA GGGCGCGCCC CAGGACCCAG GCCGGCGCGG GAAGCCAGCC CTCGGCTCCG GGTCCACAAG ACCTTCAAGT TTGTCGTCGT CGGGGTCCTG
     CCGGGCCCGT CCCGCGCGGG GTCCTGGGTC CGGCCGCGCC CTTCGGTCGG GAGCCGAGGC CCAGGTGTTC TGGAAGTTCA AACAGCAGCA GCCCCAGGAC
  68   AlaArgAla GlyArgAlaP roGlyProAr gProAlaArg GluAlaSerP roArgLeuAr gValHisLys ThrPheLysP heValValVa lGlyValLeu

 301 CTGCAGGTCG TACCTAGCTC AGCTGCAACC ATCAAACTTC ATGATCAATC AATTGGCACA CAGCAATGGG AACATAGCCC TTTGGGAGAG TTGTGTCCAC
     GACGTCCAGC ATGGATCGAG TCGACGTTGG TAGTTTGAAG TACTAGTTAG TTAACCGTGT GTCGTTACCC TTGTATCGGG AAACCCTCTC AACACAGGTG
 101 LeuGlnValV alProSerSe rAlaAlaThr IleLysLeuH isAspGlnSe rIleGlyThr GlnGlnTrpG luHisSerPr oLeuGlyGlu LeuCysProPro

 401 CAGGATCTCA TAGATCAGAA CGTCCTGGAG CCTGTAACCG GTGCACAGAG GGTGTGGGTT ACACCAATGC TTCCAACAAT TTGTTTGCTT GCCTCCCATG
     GTCCTAGAGT ATCTAGTCTT GCAGGACCTC GGACATTGGC CACGTGTCTC CCACACCCAA TGTGGTTACG AAGGTTGTTA AACAAACGAA CGGAGGGTAC
 135   GlySerHi sArgSerGlu ArgProGlyA laCysAsnAr gCysThrGlu GlyValGlyT yrThrAsnAl aSerAsnAsn LeuPheAlaC ysLeuProCys

 501 TACAGCTTGT AAATCAGATG AAGAAGAGAG AAGTCCCTGC ACCACGACCA GGAACACAGC ATGTCAGTGC AAACCAGGAA CTTTCCGGAA TGACAATTCT
     ATGTCGAACA TTTAGTCTAC TTCTTCTCTC TTCAGGGACG TGGTGCTGGT CCTTGTGTCG TACAGTCACG TTTGGTCCTT GAAAGGCCTT ACTGTTAAGA
 168   ThrAlaCys LysSerAspG luGluGluAr gSerProCys ThrThrThrA rgAsnThrAl aCysGlnCys LysProGlyT hrPheArgAs nAspAsnSer

 601 GCTGAGATGT GCCGGAAGTG CAGCACAGGG TGCCCCAGAG GGATGGTCAA GGTCAAGGAT TGTACGCCCT GGAGTGACAT CGAGTGTGTC CACAAAGAAT
     CGACTCTACA CGGCCTTCAC GTCGTGTCCC ACGGGGTCTC CCTACCAGTT CCAGTTCCTA ACATGCGGGA CCTCACTGTA GCTCACACAG GTGTTTCTTA
 201 AlaGluMetC ysArgLysCy sSerThrGly CysProArgG lyMetValLy sValLysAsp CysThrProT rpSerAspIl eGluCysVal HisLysGluSer

 701 CAGGCAATGG ACATAATATA TGGGTGATTT TGGTTGTGAC TTTGGTTGTT CCGTTGCTGT TGGTGGCTGT GCTGATTGTC TGTTGTTGCA TCGGCTCAGG
     GTCCGTTACC TGTATTATAT ACCCACTAAA ACCAACACTG AAACCAACAA GGCAACGACA ACCACCGACA CGACTAACAG ACAACAACGT AGCCGAGTCC
 235   GlyAsnGl yHisAsnIle TrpValIleL euValValTh rLeuValVal ProLeuLeuL euValAlaVa lLeuIleVal CysCysCysI leGlySerGly

 801 TTGTGGAGGG GACCCCAAGT GCATGGACAG GGTGTGTTTC TGGCGCTTGG GTCTCCTACG AGGGCCTGGG GCTGAGGACA ATGCTCACAA CGAGATTCTG
     AACACCTCCC CTGGGGTTCA CGTACCTGTC CCACACAAAG ACCGCGAACC CAGAGGATGC TCCCGGACCC CGACTCCTGT TACGAGTGTT GCTCTAAGAC
 268  CysGlyGly AspProLysC ysMetAspAr gValCysPhe TrpArgLeuG lyLeuLeuAr gGlyProGly AlaGluAspA snAlaHisAs nGluIleLeu

 901 AGCAACGCAG ACTCGCTGTC CACTTTCGTC TCTGAGCAGC AAATGGAAAG CCAGGAGCCG GCAGATTTGA CAGGTGTCAC TGTACAGTCC CCAGGGGAGG
     TCGTTGCGTC TGAGCGACAG GTGAAAGCAG AGACTCGTCG TTTACCTTTC GGTCCTCGGC CGTCTAAACT GTCCACAGTG ACATGTCAGG GGTCCCCTCC
 301 SerAsnAlaA spSerLeuSe rThrPheVal SerGluGlnG lnMetGluSe rGlnGluPro AlaAspLeuT hrGlyValTh rValGlnSer ProGlyGluAla

1001 CACAGTGTCT GCTGGGACCG GCAGAAGCTG AAGGGTCTCA GAGGAGGAGG CTGCTGGTTC CAGCAAATGG TGCTGACCCC ACTGAGACTC TGATGCTGTT
     GTGTCACAGA CGACCCTGGC CGTCTTCGAC TTCCCAGAGT CTCCTCCTCC GACGACCAAG GTCGTTTACC ACGACTGGGG TGACTCTGAG ACTACGACAA
 335   GlnCysLe uLeuGlyPro AlaGluAlaG luGlySerGl nArgArgArg LeuLeuValP roAlaAsnGl yAlaAspPro ThrGluThrL euMetLeuPhe
```

Fig. 1

```
1101 CTTTGACAAG TTTGCAAACA TCGTGCCCTT TGACTCCTGG GACCAGCTCA TGAGGCAGCT GGACCTCACG AAAAATGAGA TCGATGTGGT CAGAGCTGGT
     GAAACTGTTC AAACGTTTGT AGCACGGGAA ACTGAGGACC CTGGTCGAGT ACTCCGTCGA CCTGGAGTGC TTTTTACTCT AGCTACACCA GTCTCGACCA
368   PheAspLys PheAlaAsnI leValProPh eAspSerTrp AspGlnLeuM etArgGlnLe uAspLeuThr LysAsnGluI leAspValVa lArgAlaGly

1201 ACAGCAGGCC CAGGGGATGC CTTGTATGCA ATGCTGATGA AATGGGTCAA CAAAACTGGA CGGAACGCCT CGATCCACAC CCTGCTGGAT GCCTTGGAGA
     TGTCGTCCGG GTCCCCTACG GAACATACGT TACGACTACT TTACCCAGTT GTTTTGACCT GCCTTGCGGA GCTAGGTGTG GGACGACCTA CGGAACCTCT
401  ThrAlaGlyP roGlyAspAl aLeuTyrAla MetLeuMetL ysTrpValAs nLysThrGly ArgAsnAlaS erIleHisTh rLeuLeuAsp AlaLeuGluArg

1301 GGATGGAAGA GAGACATGCA AAAGAGAAGA TTCAGGACCT CTTGGTGGAC TCTGGAAAGT TCATCTACTT AGAAGATGGC ACAGGCTCTG CCGTGTCCTT
     CCTACCTTCT CTCTGTACGT TTTCTCTTCT AAGTCCTGGA GAACCACCTG AGACCTTTCA AGTAGATGAA TCTTCTACCG TGTCCGAGAC GGCACAGGAA
435    MetGluGl uArgHisAla LysGluLysI leGlnAspLe uLeuValAsp SerGlyLysP heIleTyrLe uGluAspGly ThrGlySerA laValSerLeu

1401 GGAGTGA
     CCTCACT
468   GluOP*
```

Fig. 1 (cont.)

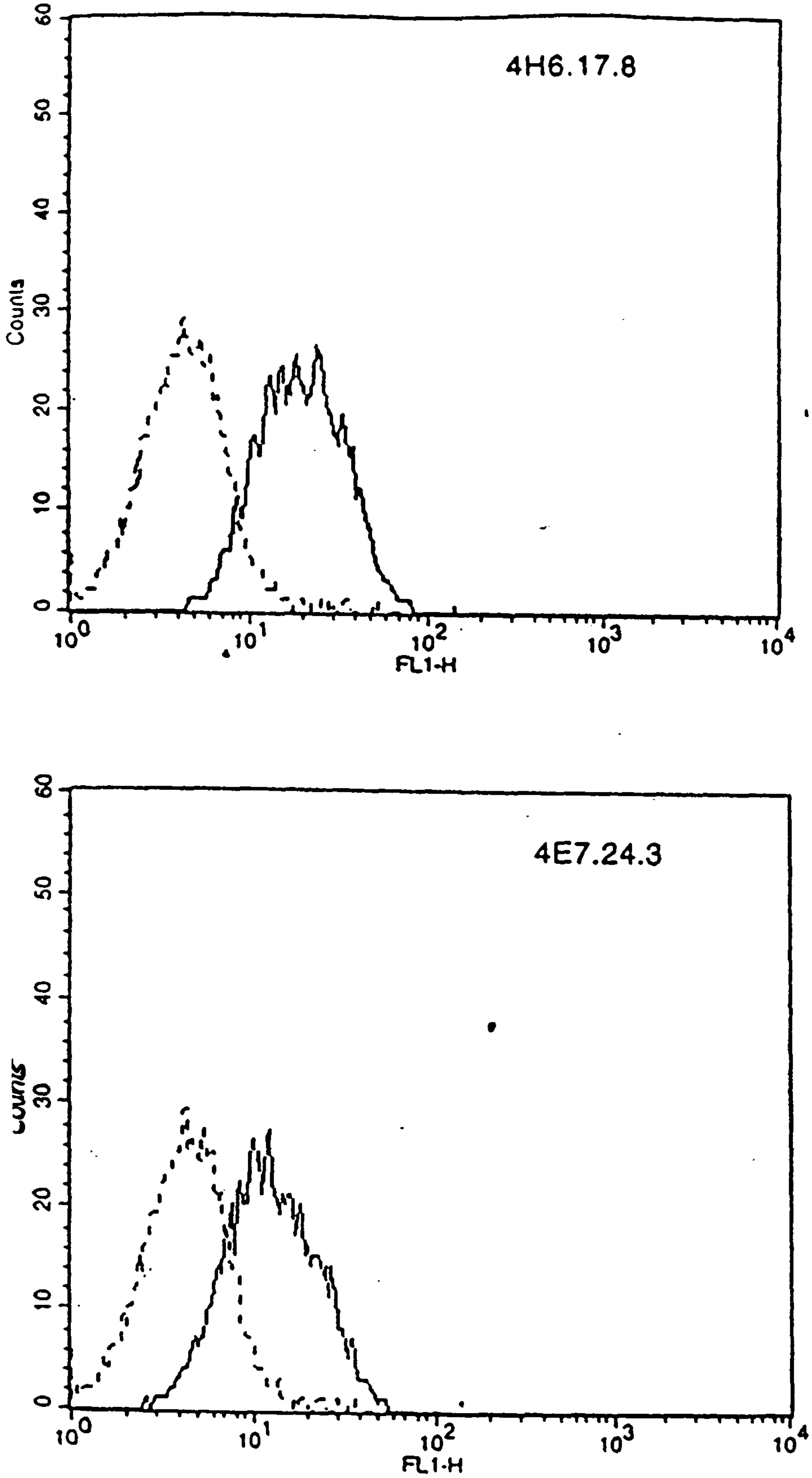
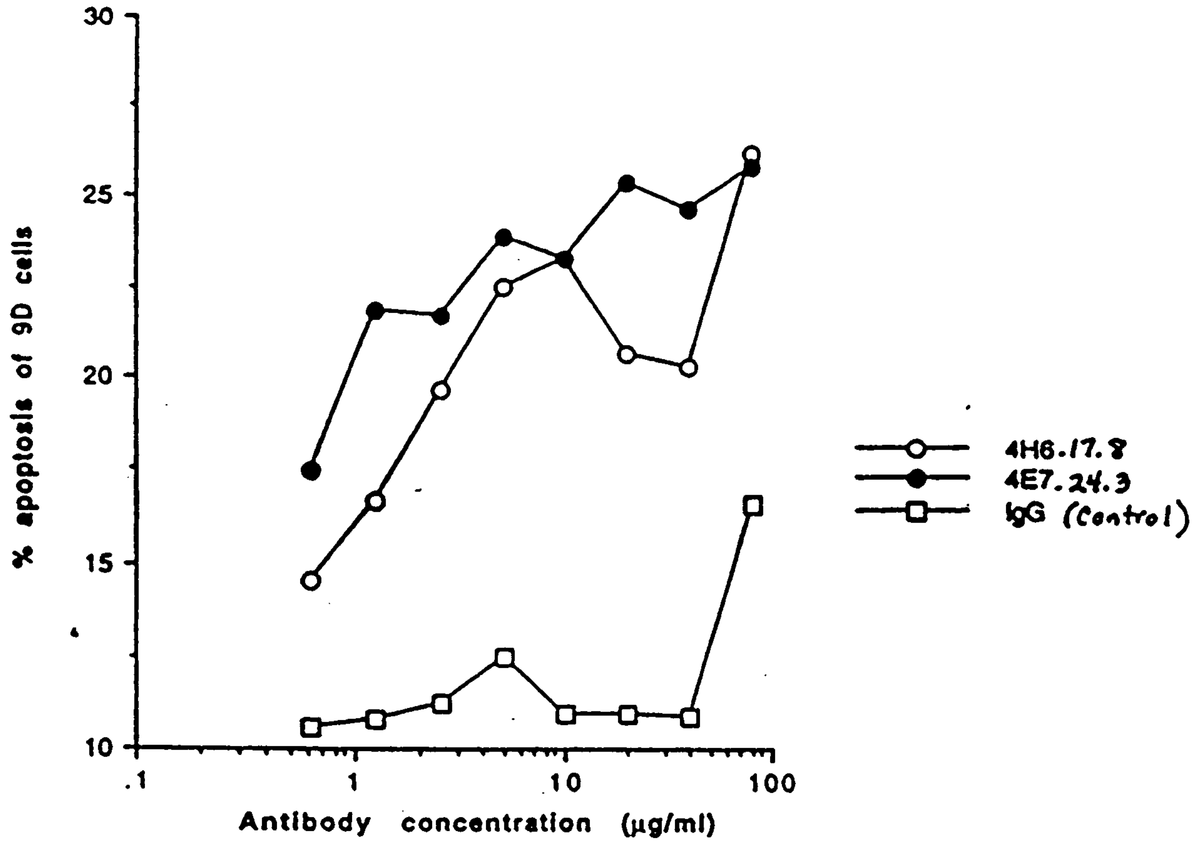


Fig. 2



30
25
20
15
10
% apoptosis of 9D cells
.1
1
10
100
Antibody concentration (µg/ml)
4H6.17.8
4E7.24.3
IgG (Control)

Fig. 3

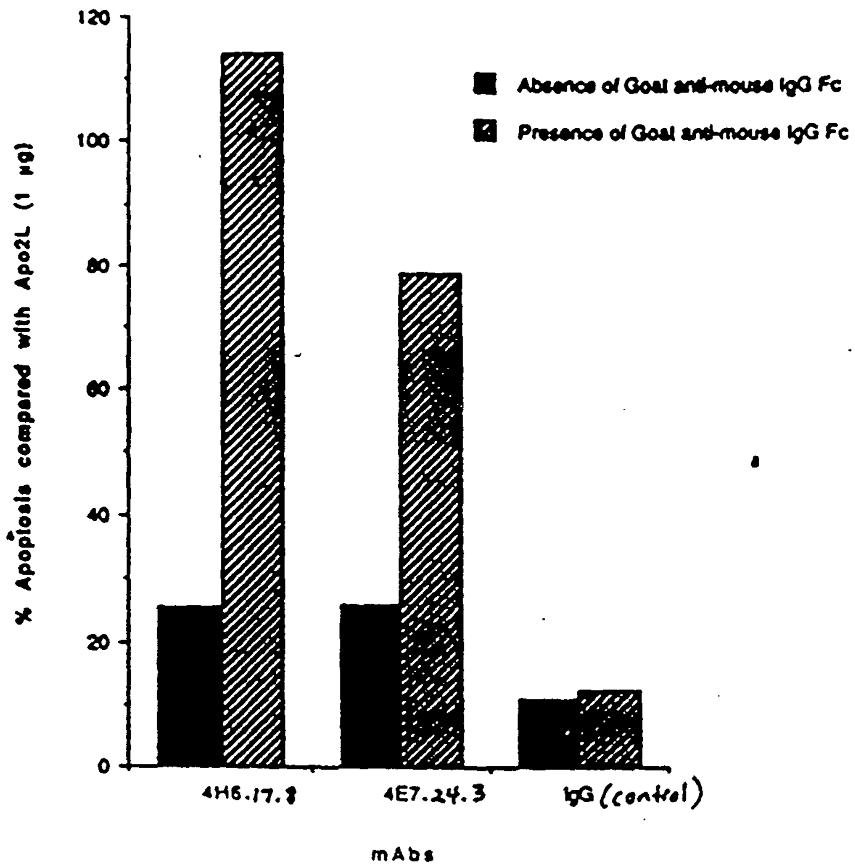

120
100
80
60
40
20
0
% Apoptosis compared with Apo2L (1 µg)
Absence of Goat anti-mouse IgG Fc
Presence of Goat anti-mouse IgG Fc
4H6.17.8
4E7.24.3
IgG (control)
mAbs

Fig. 4

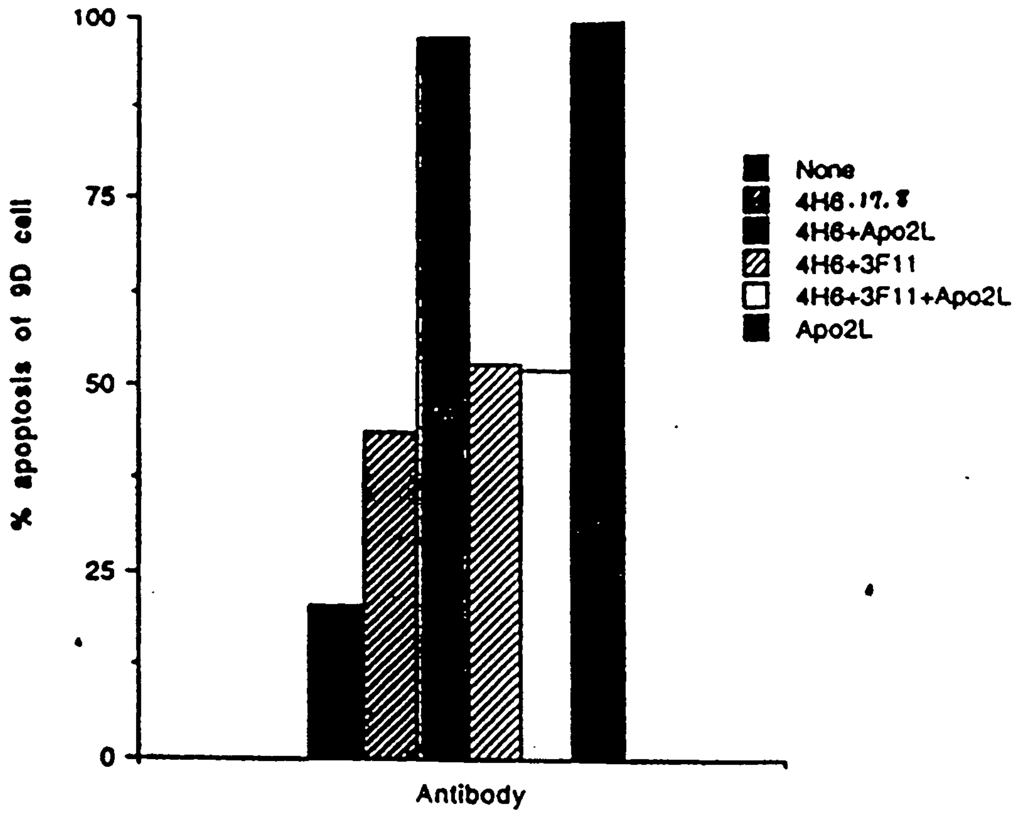
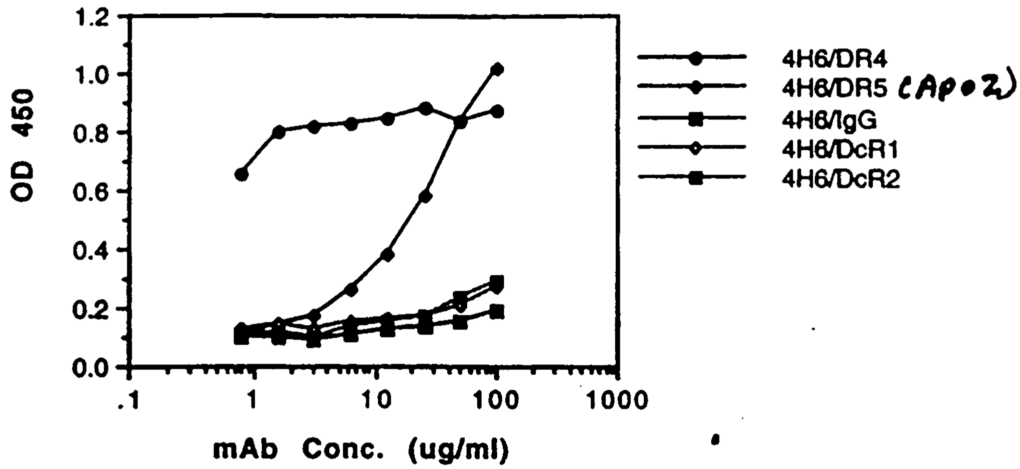

100
75
50
25
0
% apoptosis of 9D cell
Antibody
None
4H6.17.8
4H6+Apo2L
4H6+3F11
4H6+3F11+Apo2L
Apo2L

Fig. 5

4H6: Binding to receptors for Apo2L



4E7: Binding to Receptors for Apo2L

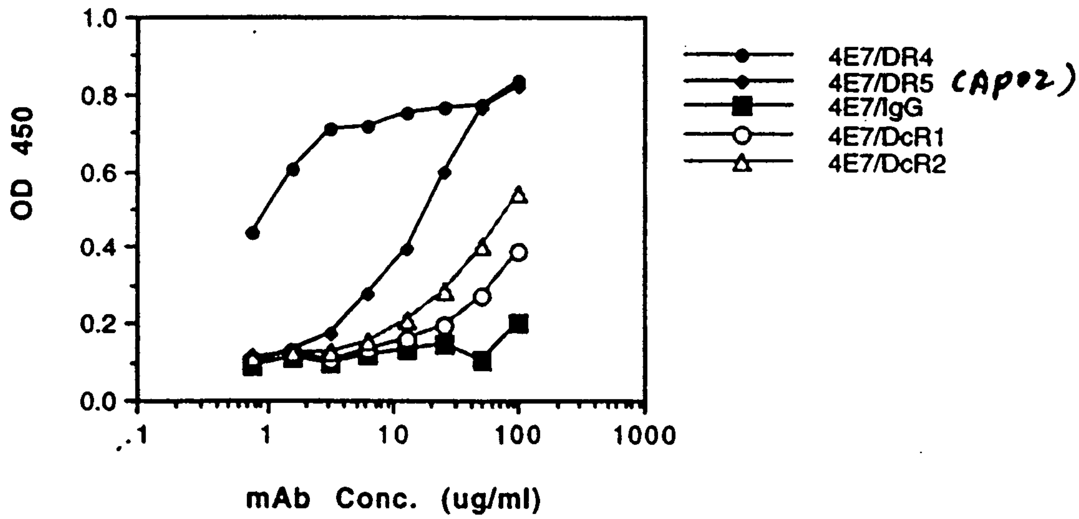


Fig. 6

Affinities of Apo2Rs and mAbs

		Affinity (pM)
DR4-IgG	to Apo2L	82
DR5-IgG	to Apo2L	1
mAb 4E7	to DR4-IgG	2
mAb 4H6	to "	5
mAb 5G11	to "	22
mAb 3F11	to DR5-IgG	20
mAb 3H3	to "	3

Affinlties were determined using KinExA

Fig. 7

Apoptosi of 9D c lls by anti-DR4 mAbs plus compl ments or goat anti-mous Ig-FC

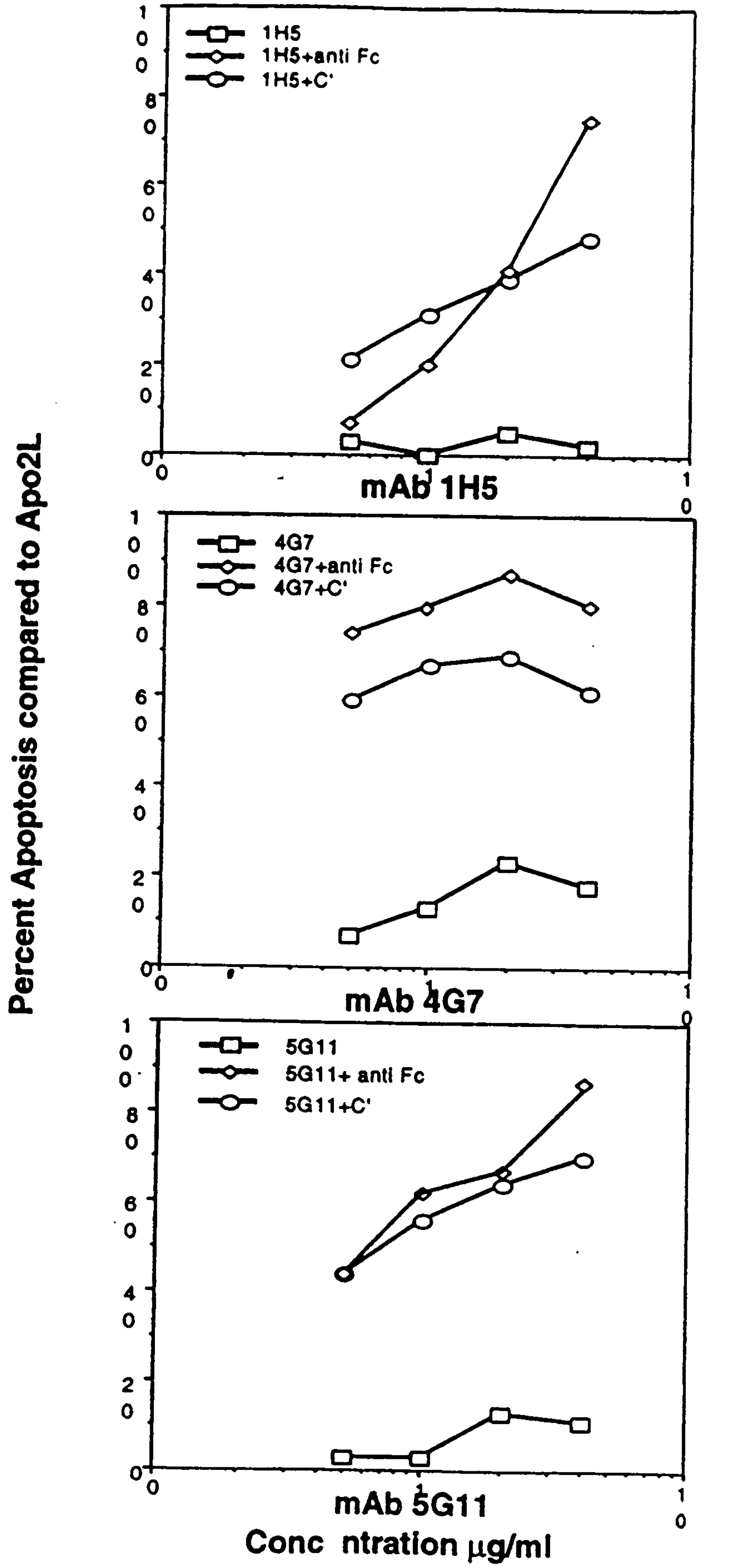
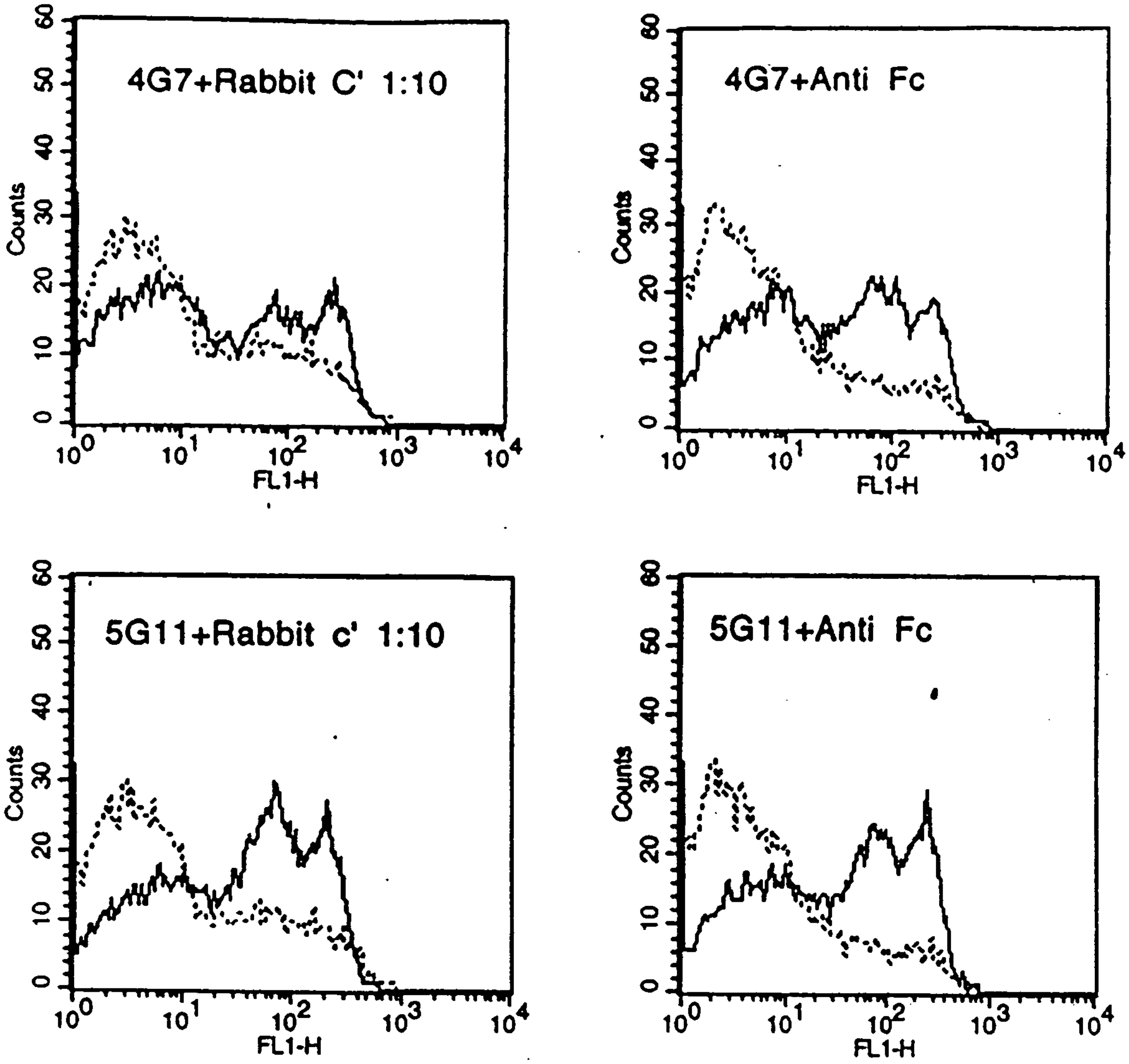


Fig. 8A


4G7+Rabbit C' 1:10
4G7+Anti Fc
5G11+Rabbit c' 1:10
5G11+Anti Fc
Counts
FL1-H

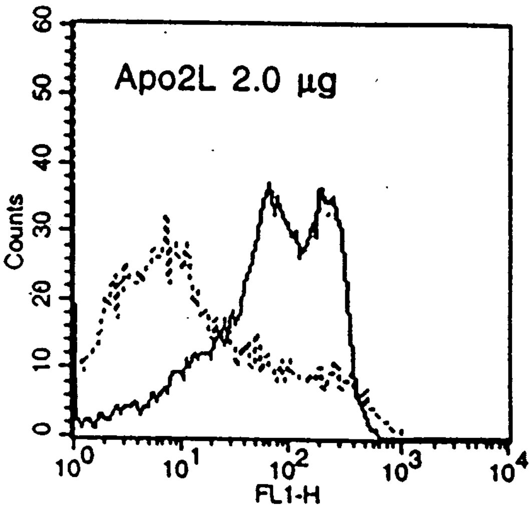

Apo2L 2.0 µg
Counts
FL1-H

Fig. 8B

Fig. 9

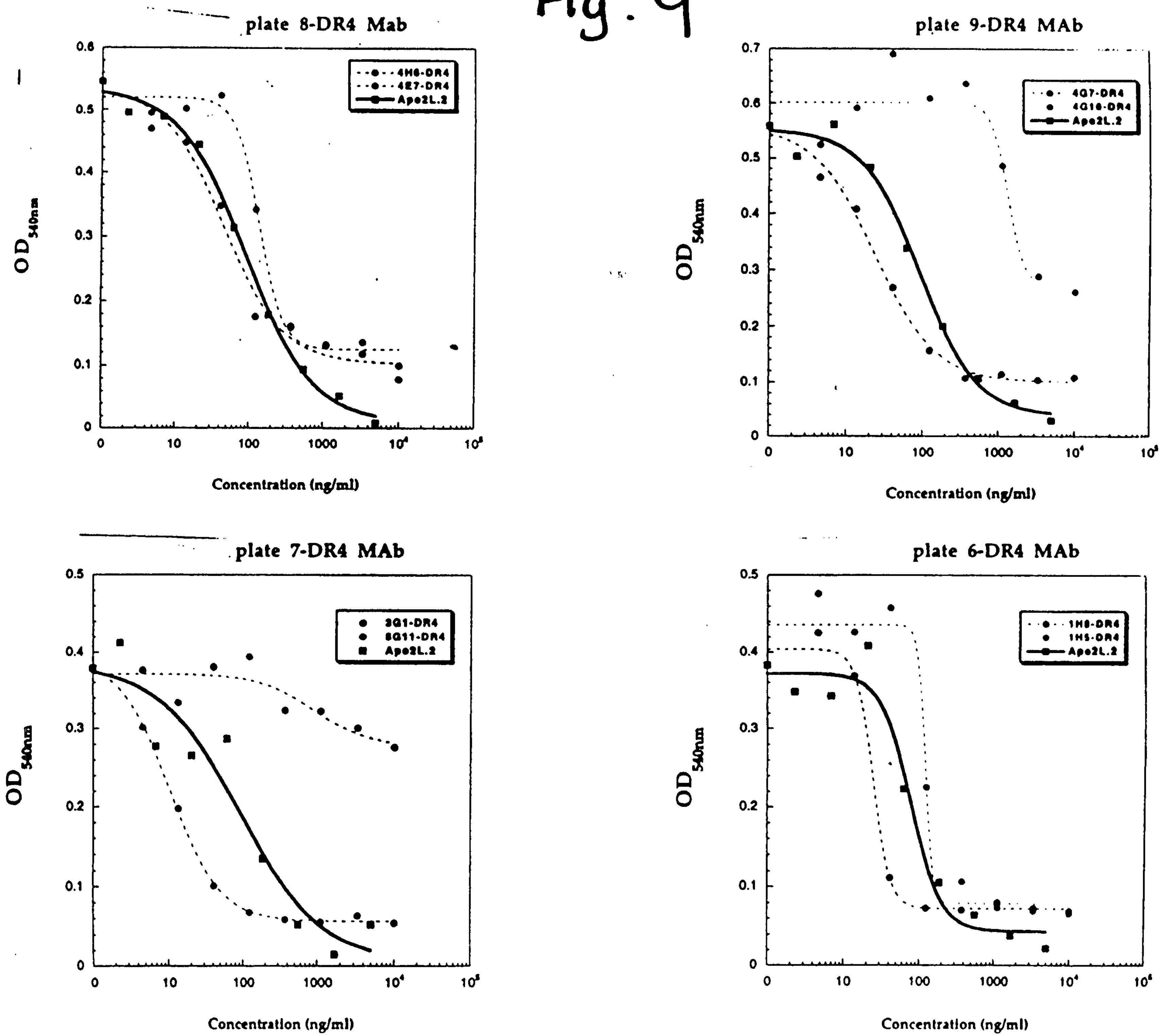


plate 8-DR4 Mab
4H6-DR4
4E7-DR4
Apo2L.2
OD540nm
Concentration (ng/ml)
plate 9-DR4 MAb
4G7-DR4
4G10-DR4
Apo2L.2
OD540nm
Concentration (ng/ml)
plate 7-DR4 MAb
3G1-DR4
5G11-DR4
Apo2L.2
OD540nm
Concentration (ng/ml)
plate 6-DR4 MAb
1H6-DR4
1H5-DR4
Apo2L.2
OD540nm
Concentration (ng/ml)

Apoptosis of anti DR4 mAbs plus goat anti FcAb

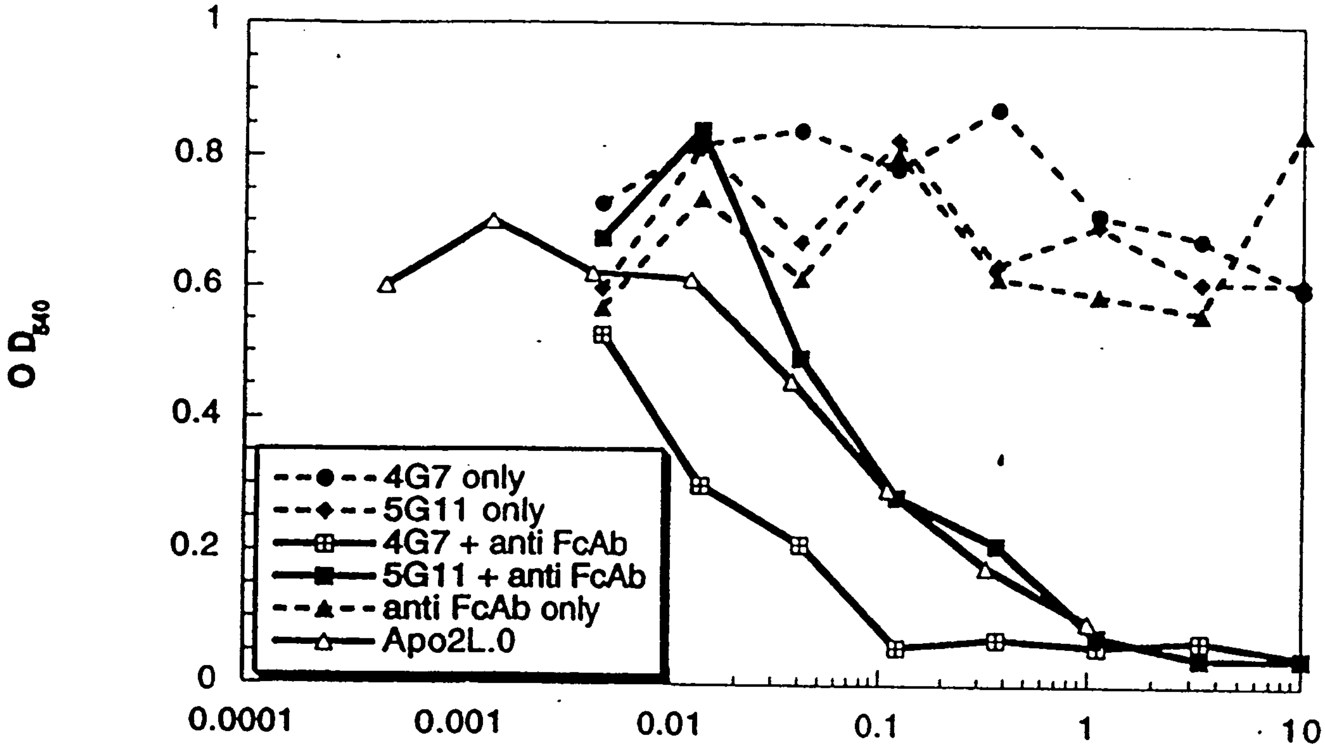


Fig. 10 A

Apoptosis induced by anti DR4 mAbs plus Complements

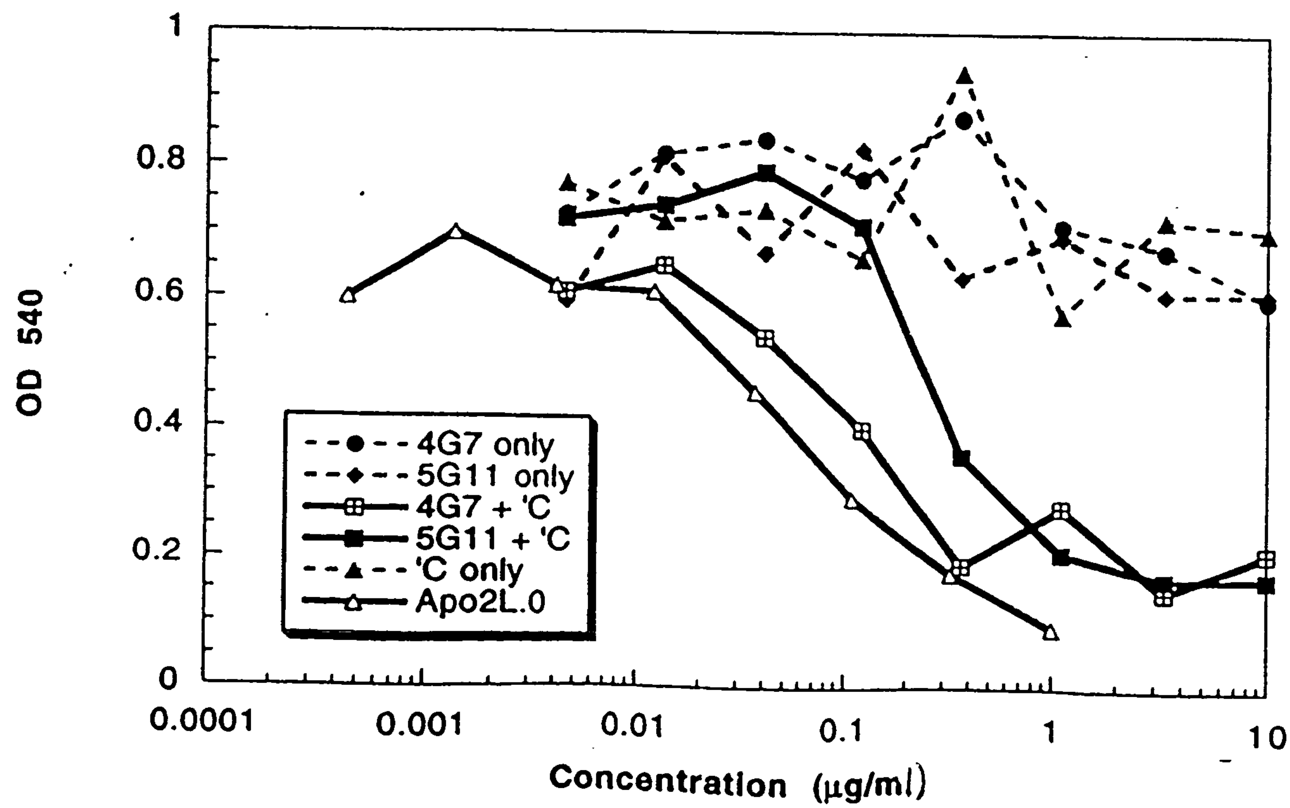


Fig. 10B

Effect of anti DR4 MAb with complement on HCT 116

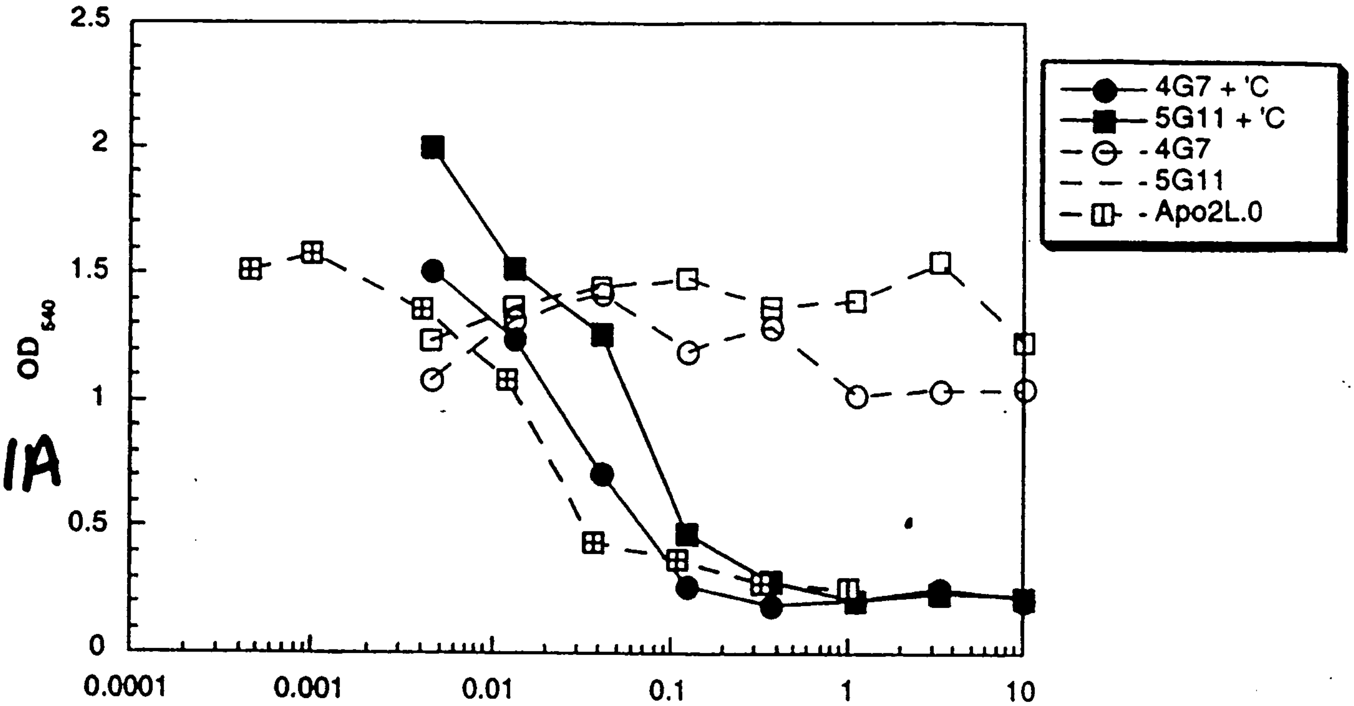


Fig. 11A

Effect of anti DR4 MAb with anti-IgFc on HCT 116

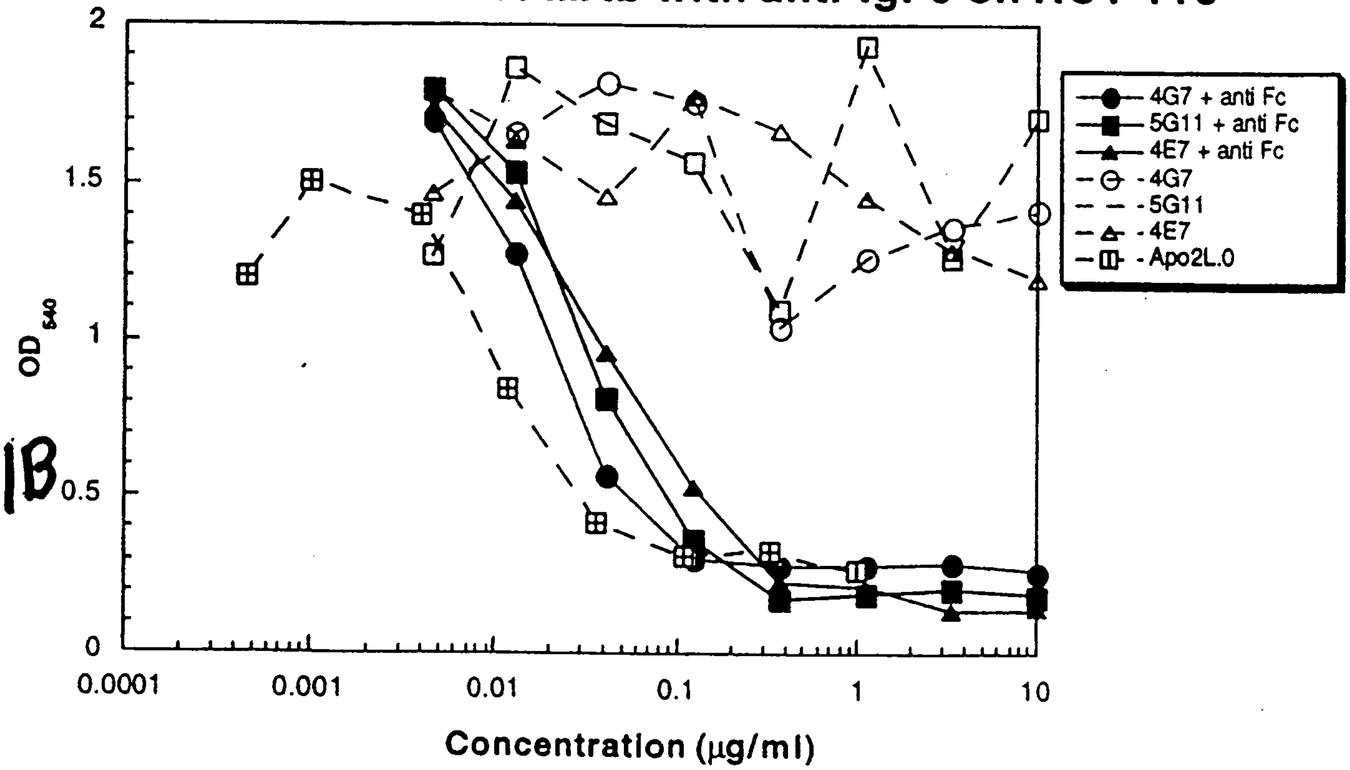


Fig. 11B

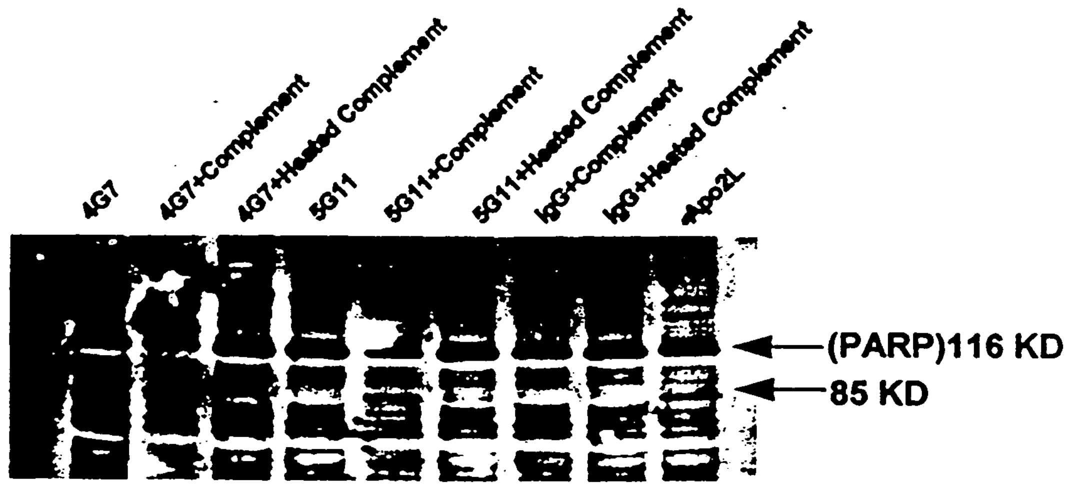
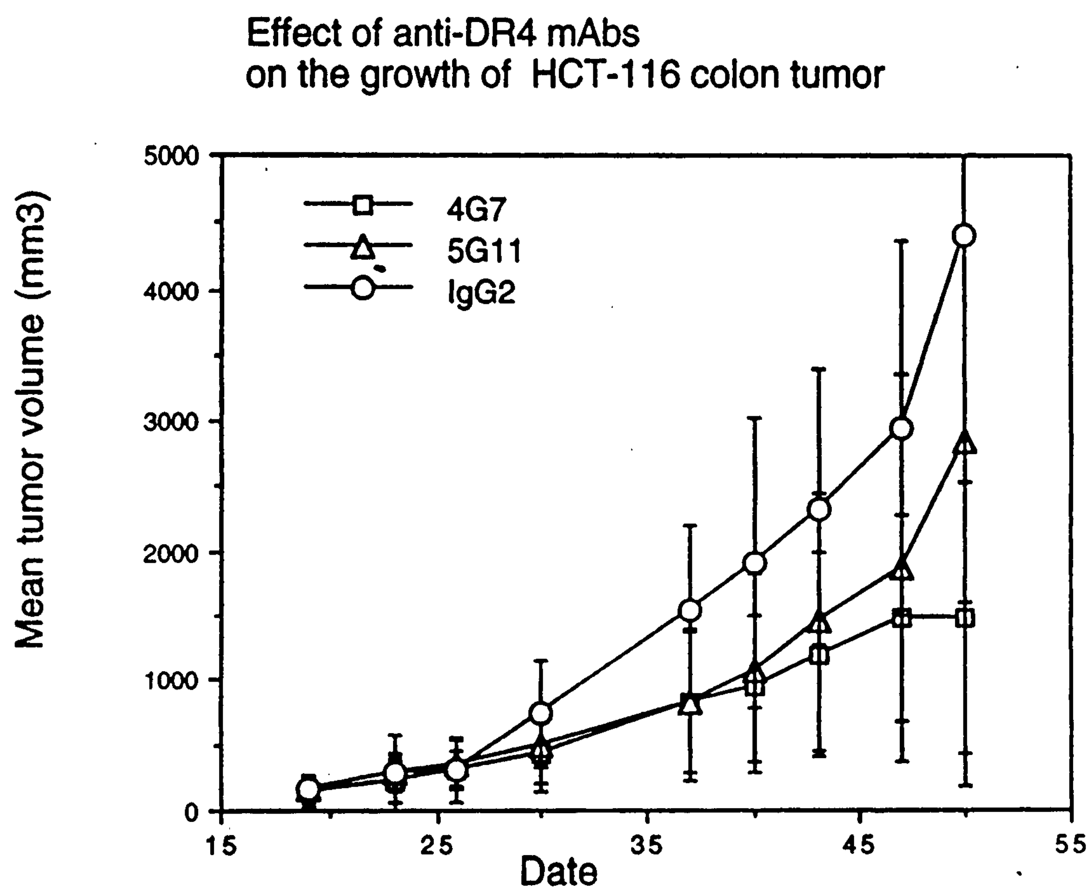

4G7
4G7+Complement
4G7+Heated Complement
5G11
5G11+Complement
5G11+Heated Complement
IgG+Complement
IgG+Heated Complement
sApo2L
(PARP)116 KD
85 KD

Fig. 12



Effect of anti-DR4 mAbs
on the growth of HCT-116 colon tumor
4G7
5G11
IgG2
Mean tumor volume (mm3)
5000
4000
3000
2000
1000
0
15
25
35
45
55
Date

Fig. 13

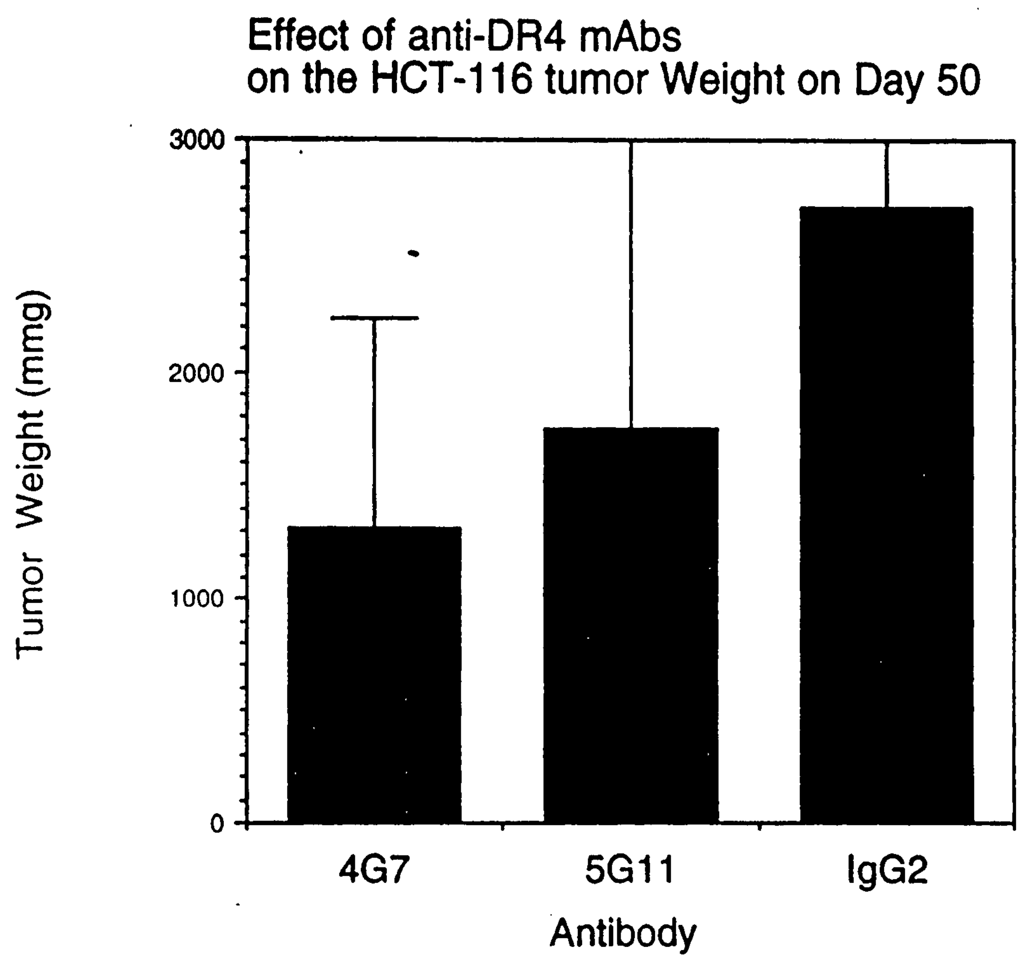
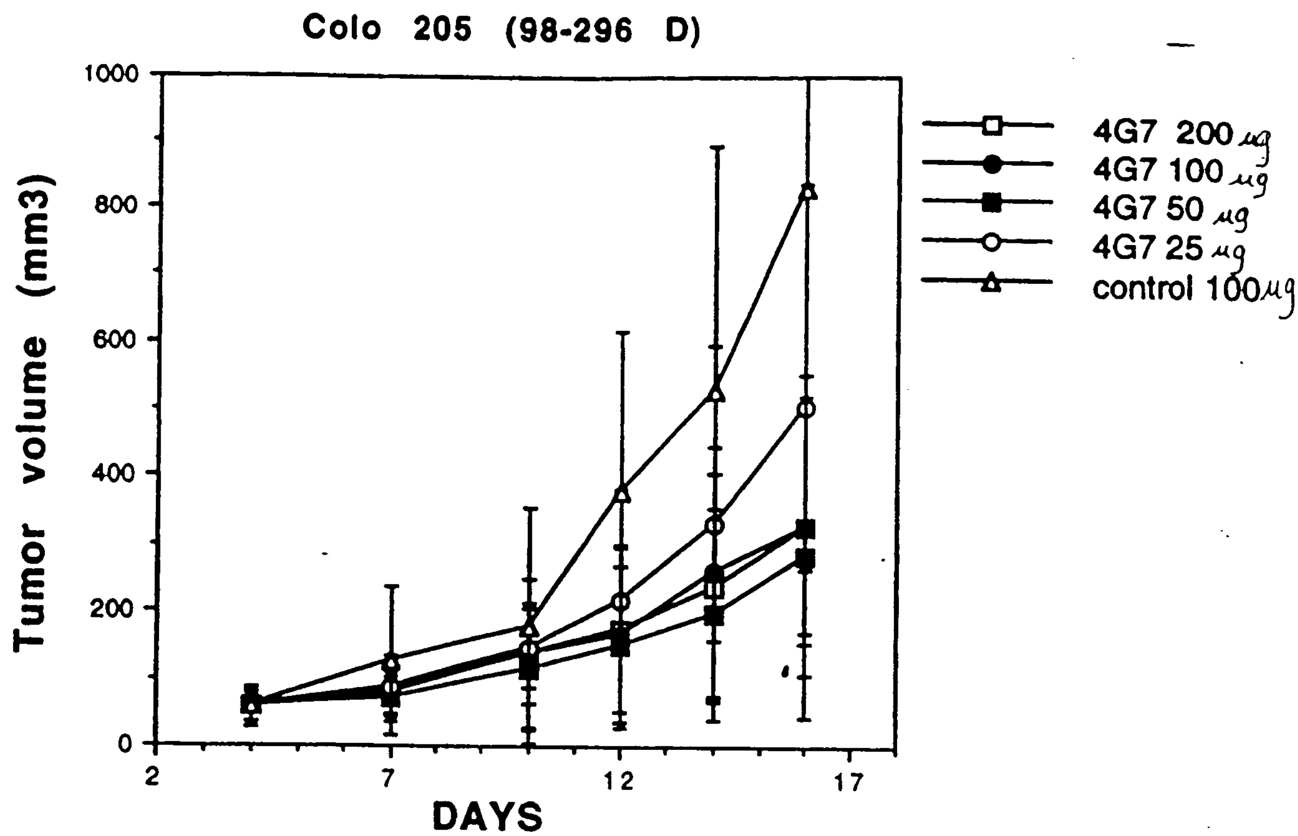

Effect of anti-DR4 mAbs
on the HCT-116 tumor Weight on Day 50
3000
2000
1000
0
Tumor Weight (mmg)
4G7
5G11
IgG2
Antibody

Fig. 14


Colo 205 (98-296 D)
1000
800
600
400
200
0
Tumor volume (mm3)
2
7
12
17
DAYS
4G7 200 ug
4G7 100 ug
4G7 50 ug
4G7 25 ug
control 100ug

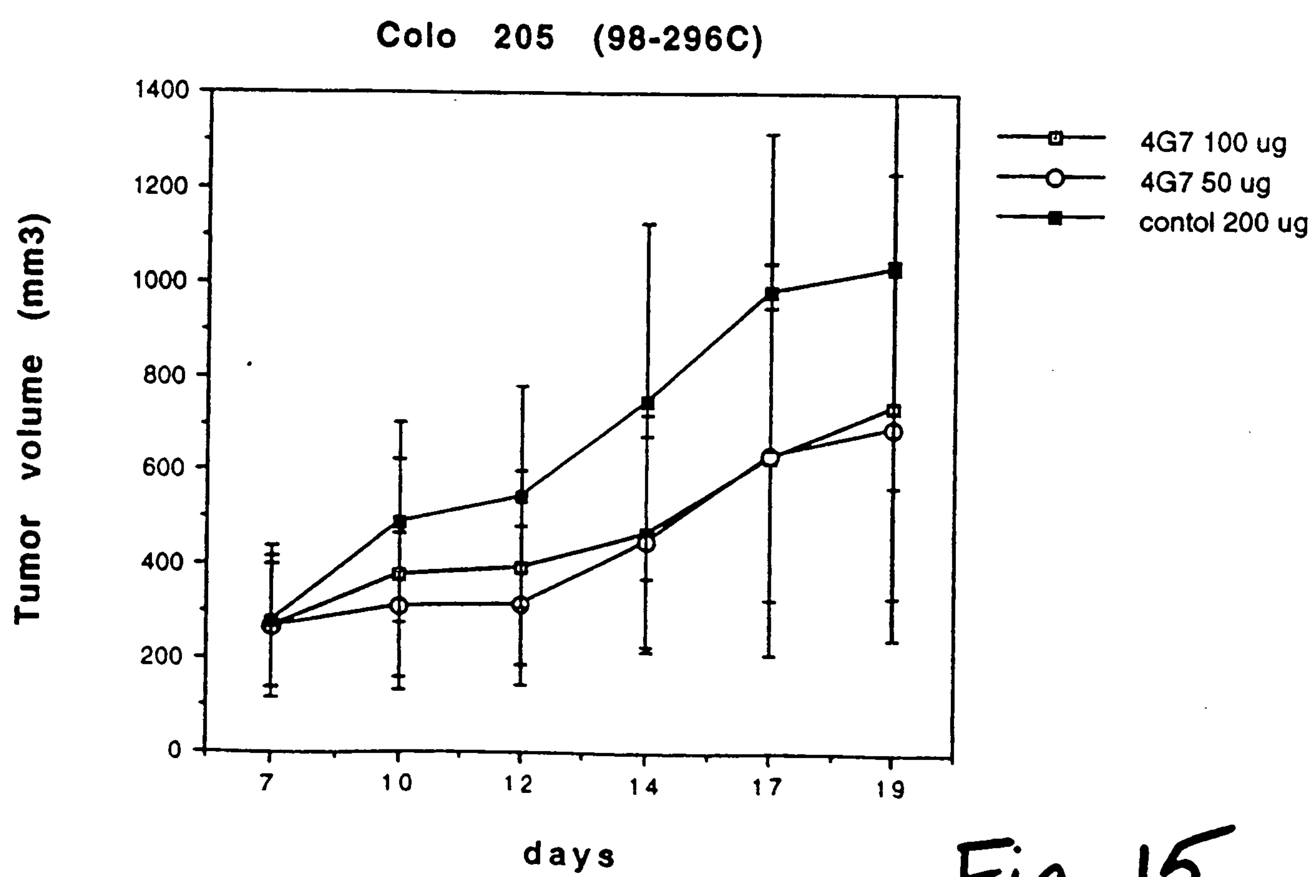
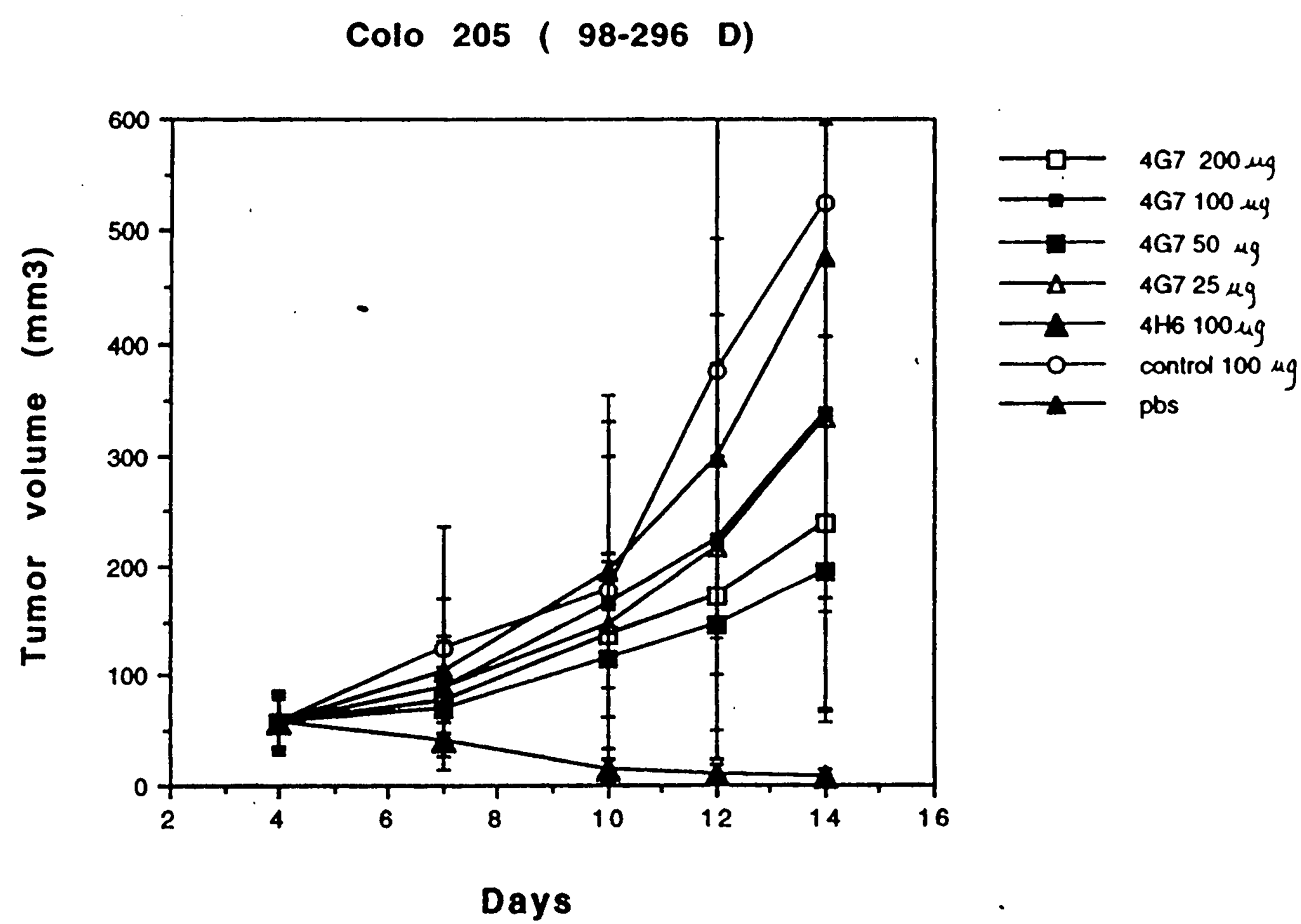

Colo 205 (98-296C)
1400
1200
1000
800
600
400
200
0
Tumor volume (mm3)
7
10
12
14
17
19
days
4G7 100 ug
4G7 50 ug
contol 200 ug

Fig. 15



Colo 205 (98-296 D)
Tumor volume (mm3)
600
500
400
300
200
100
0
2
4
6
8
10
12
14
16
Days
4G7 200 µg
4G7 100 µg
4G7 50 µg
4G7 25 µg
4H6 100µg
control 100 µg
pbs

Fig. 16

General Characteristics of Anti-DR4 mAbs

	Isotype	Kd-1 (pM)	Apop w/o L	Apop + &Fc	Apop + C'	Block	Cross reactivity DR4	DR5	DCR1	DCR2
1H5.24.9	IgG2a			-	-	ND	+++	-	-	-
1H8.17.5	IgG1			+	ND	ND	+++	-	-	-
3G1.17.2	IgG1		-	-	ND	-	+++	-	-	-
4E7.24.3	IgG1	2	+/-	+	-	-	+++	+	-	+/-
4G7.18.8	IgG2a		+/-	+	+	-	+++	-	-	-
4H6.17.8	IgG1	5	+/-	+	-	+	+++	+	-	-
4G10.20.6	IgG1			+	ND	-	+++	+	-	-
5G11.17.1	IgG2b	22		+	+	ND	+++	++	-	-

All these mAbs recognize DR4 on 9D cells and immune precipitate DR4-IgG.
w/o L : The apoptotic ability of mAbs by themselves was detected on 9D cells, skmes cells , HCT116 and colo 205
+ &FC: The apoptotic ability of mAbs was determined in combination with goat anti-mouse IgG FC.
+ C' : The apoptotic ability of mAbs was determined in the presence of rabbit complement
Degrees of binding (+) to DR5 by Mabs 4E7 and 4H6 at 10 ug/ml are 15% of the binding to DR4.

Fig. 17

```
< 4H6ApDR1
< 4H6 Anti DR4, Murine variable, Human kappaconstant
<  ELEMENT: Component (start: 1557/1559; end: 5390/5390)
< length: 702

 929 AT GGGATGGTCA TGTATCATCC TTTTTCTAGT AGCAACTGCA
     TA CCCTACCAGT ACATAGTAGG AAAAAGATCA TCGTTGACGT
   1 M   G  W  S   C  I  I  L   F  L  V   A  T  A
     ^Signal Sequence

 971 ACTGGAGTAC ATTCAGATAT CCAGATGACA CAGACTACAT CCTCCCTGTC
     TGACCTCATG TAAGTCTATA GGTCTACTGT GTCTGATGTA GGAGGGACAG
  15 T  G  V  H   S  D  I   Q  M  T   Q  T  T  S   S  L  S
                    ^D is first amino acid of variable
                                  FR1

1021 TGCCTCTCTG GGAGACAGAG TCACCATCAG TTGCAGGGCA AGTCAGGACA
     ACGGAGAGAC CCTCTGTCTC AGTGGTAGTC AACGTCCCGT TCAGTCCTGT
  32  A  S  L   G  D  R  V   T  I  S   C  R  A   S  Q  D  I
               FR1                               CDR1

1071 TTAGCAATTA TTTAAACTGG TATCAGCGGA AACCAGATGG AACTGTTAAA
     AATCGTTAAT AAATTTGACC ATAGTCGCCT TTGGTCTACC TTGACAATTT
  49  S  N  Y   L  N  W   Y  Q  R  K   P  D  G   T  V  K
        CDR1                      FR2

1121 CTCCTGATCT ACTACACATC ACGATTACAC TCAGGAGTCC CATCACGGTT
     GAGGACTAGA TGATGTGTAG TGCTAATGTG AGTCCTCAGG GTAGTGCCAA
  65 L  L  I  Y   Y  T  S   R  L  H   S  G  V  P   S  R  F
       FR2            CDR2                   FR3
```

Fig. 18A

```
                              FR3
1171 CAGTGGCAGT GGGTCTGGAA CAGATTATTC TCTCACCATT AGCAACCTGG
     GTCACCGTCA CCCAGACCTT GTCTAATAAG AGAGTGGTAA TCGTTGGACC
  82  S  G  S   G  S  G  T   D  Y  S   L  T  I   S  N  L  E

1221 AACAAGAAGA TATTGCCACT TACTTTTGCC AACAGGGTAA TACGCTTCCA
     TTGTTCTTCT ATAACGGTGA ATGAAAACGG TTGTCCCATT ATGCGAAGGT
  99  Q  E  D   I  A  T   Y  F  C  Q   Q  G  N   T  L  P
            FR3                             CDR3

1271 TTCACGTTCG GCTCGGCCAC CAAGCTGGAA CTAACTCGGA CCGTGGCTGC
     AAGTGCAAGC CGAGCCGGTG GTTCGACCTT GATTGAGCCT GGCACCGACG
 115 F  T  F  G   S  A  T   K  L  E   L  T  R  T   V  A  A
  CDR3           FR4                             CH1

1321 ACCATCTGTC TTCATCTTCC CGCCATCTGA TGAGCAGTTG AAATCTGGAA
     TGGTAGACAG AAGTAGAAGG GCGGTAGACT ACTCGTCAAC TTTAGACCTT
 132  P  S  V   F  I  F  P   P  S  D   E  Q  L   K  S  G  T
                             CH1

1371 CTGCCTCTGT TGTGTGCCTG CTGAATAACT TCTATCCCAG AGAGGCCAAA
     GACGGAGACA ACACACGGAC GACTTATTGA AGATAGGGTC TCTCCGGTTT
 149  A  S  V   V  C  L   L  N  N  F   Y  P  R   E  A  K
                             CH1

1421 GTACAGTGGA AGGTGGATAA CGCCCTCCAA TCGGGTAACT CCCAGGAGAG
     CATGTCACCT TCCACCTATT GCGGGAGGTT AGCCCATTGA GGGTCCTCTC
 165 V  Q  W  K   V  D  N   A  L  Q   S  G  N  S   Q  E  S
                             CH1

1471 TGTCACAGAG CAGGACAGCA AGGACAGCAC CTACAGCCTC AGCAGCACCC
     ACAGTGTCTC GTCCTGTCGT TCCTGTCGTG GATGTCGGAG TCGTCGTGGG
 182  V  T  E   Q  D  S  K   D  S  T   Y  S  L   S  S  T  L
                             CH1

1521 TGACGCTGAG CAAAGCAGAC TACGAGAAAC ACAAAGTCTA CGCCTGCGAA
```

Fig. 18B

```
     ACTGCGACTC GTTTCGTCTG ATGCTCTTTG TGTTTCAGAT GCGGACGCTT
 199  T  L  S   K  A  D   Y  E  K  H   K  V  Y   A  C  E
                               CHI
1571 GTCACCCATC AGGGCCTGAG CTCGCCCGTC ACAAAGAGCT TCAACAGGGG
     CAGTGGGTAG TCCCGGACTC GAGCGGGCAG TGTTTCTCGA AGTTGTCCCC
 215 V  T  H  Q   G  L  S   S  P  V   T  K  S  F   N  R  G
                              CHI
1621 AGAGTGTTAA
     TCTCACAATT
 232  E  C  O
```

Fig. 18C

```
<  humanized MaE11 version 1 HEAVY CHAIN
< 4H6 Anti DR4, murine variable, Human IgG1 heavy constant
< 4H6Amonomer
< length: 1431

 930 A TGGGATGGTC ATGTATCATC CTTTTTCTAG TAGCAACTGC
     T ACCCTACCAG TACATAGTAG GAAAAAGATC ATCGTTGACG
   1 M   G  W  S   C  I  I   L  F  L  V   A  T  A
     ^ signal sequence

 971 AACTGGAGTA CATTCAGAAG TTCAGCTGAA GGAGTCAGGA CCTGGCCTGG
     TTGACCTCAT GTAAGTCTTC AAGTCGACTT CCTCAGTCCT GGACCGGACC
  15  T  G  V   H  S  E  V   Q  L  K   E  S  G   P  G  L  V
                       ^E is amino acid 1 of variable heavy
                                   FR1

1021 TGGCGCCCTC ACAGAGCCTG TCCATCACTT GCACTGTCTC TGGGTTTTCA
     ACCGCGGGAG TGTCTCGGAC AGGTAGTGAA CGTGACAGAG ACCCAAAAGT
  32  A  P  S   Q  S  L   S  I  T  C   T  V  S   G  F  S
                                FR1
1071 TTAACCAGCT ATGGTGTACA CTGGGTTCGC CAGCCTCCAG GAAAGGGTCT
     AATTGGTCGA TACCACATGT GACCCAAGCG GTCGGAGGTC CTTTCCCAGA
  48 L  T  S  Y   G  V  H   W  V  R   Q  P  P  G   K  G  L
               CDR1                      FR2

1121 GGAGTGGCTG GGAGTAATAT GGGCTGTTGG AAGCACAAAT TATAATTCGG
     CCTCACCGAC CCTCATTATA CCCGACAACC TTCGTGTTTA ATATTAAGCC
  65  E  W  L   G  V  I  W   A  V  G   S  T  N   Y  N  S  A
        FR2                     CDR2

1171 CTCTCATGTC CAGACTGAGC ATCAGCAAAG ACAACTCCAA GAGCCAAGTT
```

Fig. 18D

```
     GAGAGTACAG GTCTGACTCG TAGTCGTTTC TGTTGAGGTT CTCGGTTCAA
  82  L  M  S   R  L  S   I  S  K  D   N  S  K   S  Q  V
       CDR2                      FR3

1221 TTCTTAAAAA TGAACAGTCT GCAAACTGAT GACACAGCCA TGTACTACTG
     AAGAATTTTT ACTTGTCAGA CGTTTGACTA CTGTGTCGGT ACATGATGAC
  98 F  L  K  M   N  S  L   Q  T  D   D  T  A  M   Y  Y  C
                              FR3
1271 TGCCAGAGAG GGGGAATTCG ATTACTACGG TAGTAGTCTC CTATCTTACC
     ACGGTCTCTC CCCCTTAAGC TAATGATGCC ATCATCAGAG GATAGAATGG
 115  A  R  E   G  E  F  D   Y  Y  G   S  S  L   L  S  Y  H
     FR3                       CDR3

1321 ATTCTATGAA CTTCTGGGGT CAAGGAACCT CAGTCACCGT CTCCTCAGCC
     TAAGATACTT GAAGACCCCA GTTCCTTGGA GTCAGTGGCA GAGGAGTCGG
 132  S  M  N   F  W  G   Q  G  T  S   V  T  V   S  S  A
        CDR3                  FR4                    CH1

1371 AAAACGACGG GCCCATCGGT CTTCCCCCTG GCACCCTCCT CCAAGAGCAC
     TTTTGCTGCC CGGGTAGCCA GAAGGGGGAC CGTGGGAGGA GGTTCTCGTG
 148 K  T  T  G   P  S  V   F  P  L   A  P  S  S   K  S  T

                              CH1

1421 CTCTGGGGGC ACAGCGGCCC TGGGCTGCCT GGTCAAGGAC TACTTCCCCG
     GAGACCCCCG TGTCGCCGGG ACCCGACGGA CCAGTTCCTG ATGAAGGGGC
 165  S  G  G   T  A  A  L   G  C  L   V  K  D   Y  F  P  E
                              CH1
1471 AACCGGTGAC GGTGTCGTGG AACTCAGGCG CCCTGACCAG CGGCGTGCAC
     TTGGCCACTG CCACAGCACC TTGAGTCCGC GGGACTGGTC GCCGCACGTG
 182  P  V  T   V  S  W   N  S  G  A   L  T  S   G  V  H
                              CH1
```

Fig. 18E

```
1521 ACCTTCCCGG CTGTCCTACA GTCCTCAGGA CTCTACTCCC TCAGCAGCGT
     TGGAAGGGCC GACAGGATGT CAGGAGTCCT GAGATGAGGG AGTCGTCGCA
 198 T  F  P  A   V  L  Q   S  S  G   L  Y  S  L   S  S  V
                              CH1
1571 GGTGACTGTG CCCTCTAGCA GCTTGGGCAC CCAGACCTAC ATCTGCAACG
     CCACTGACAC GGGAGATCGT CGAACCCGTG GGTCTGGATG TAGACGTTGC
 215  V  T  V   P  S  S  S   L  G  T   Q  T  Y   I  C  N  V
                              CH1
1621 TGAATCACAA GCCCAGCAAC ACCAAGGTGG ACAAGAAAGT TGAGCCCAAA
     ACTTAGTGTT CGGGTCGTTG TGGTTCCACC TGTTCTTTCA ACTCGGGTTT
 232  N  H  K   P  S  N   T  K  V  D   K  K  V   E  P  K
                              CH1
1671 TCTTGTGACA AAACTCACAC ATGCCCACCG TGCCCAGCAC CTGAACTCCT
     AGAACACTGT TTTGAGTGTG TACGGGTGGC ACGGGTCGTG GACTTGAGGA
 248 S  C  D  K   T  H  T   C  P  P   C  P  A  P   E  L  L
                              CH1
1721 GGGGGGACCG TCAGTCTTCC TCTTCCCCCC AAAACCCAAG GACACCCTCA
     CCCCCCTGGC AGTCAGAAGG AGAAGGGGGG TTTTGGGTTC CTGTGGGAGT
 265  G  G  P   S  V  F  L   F  P  P   K  P  K   D  T  L  M
                              CH2
1771 TGATCTCCCG GACCCCTGAG GTCACATGCG TGGTGGTGGA CGTGAGCCAC
     ACTAGAGGGC CTGGGGACTC CAGTGTACGC ACCACCACCT GCACTCGGTG
 282  I  S  R   T  P  E   V  T  C  V   V  V  D   V  S  H
                              CH2
1821 GAAGACCCTG AGGTCAAGTT CAACTGGTAC GTGGACGGCG TGGAGGTGCA
     CTTCTGGGAC TCCAGTTCAA GTTGACCATG CACCTGCCGC ACCTCCACGT
 298 E  D  P  E   V  K  F   N  W  Y   V  D  G  V   E  V  H
                              CH2
1871 TAATGCCAAG ACAAAGCCGC GGGAGGAGCA GTACAACAGC ACGTACCGGG
     ATTACGGTTC TGTTTCGGCG CCCTCCTCGT CATGTTGTCG TGCATGGCCC
 315  N  A  K   T  K  P  R   E  E  Q   Y  N  S   T  Y  R  V
                              CH2
```

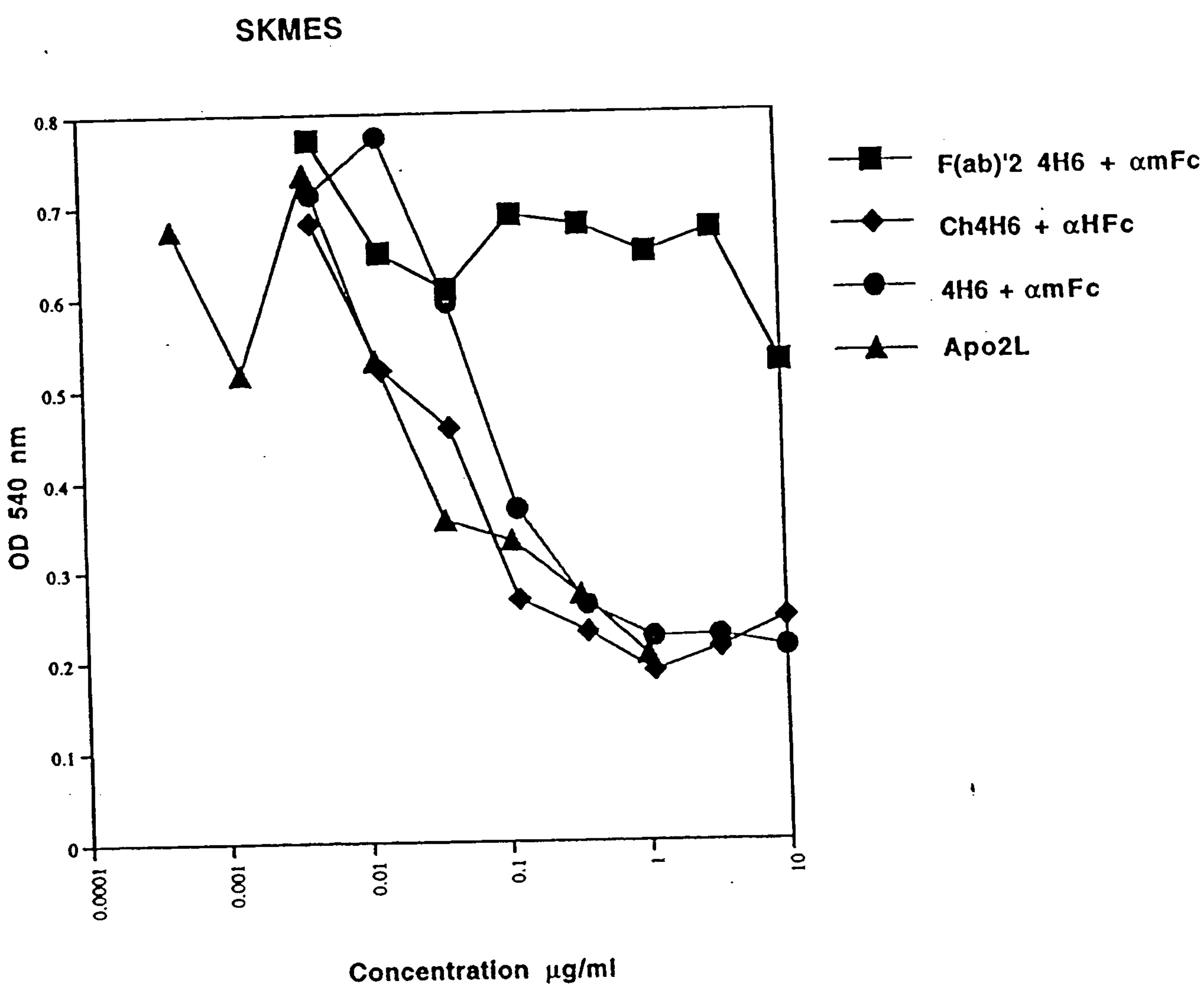
Fig. 18F

```
1921 TGGTCAGCGT CCTCACCGTC CTGCACCAGG ACTGGCTGAA TGGCAAGGAG
     ACCAGTCGCA GGAGTGGCAG GACGTGGTCC TGACCGACTT ACCGTTCCTC
332    V  S  V   L  T  V   L  H  Q  D   W  L  N   G  K  E
                              CH2
1971 TACAAGTGCA AGGTCTCCAA CAAAGCCCTC CCAGCCCCCA TCGAGAAAAC
     ATGTTCACGT TCCAGAGGTT GTTTCGGGAG GGTCGGGGGT AGCTCTTTTG
348  Y  K  C  K   V  S  N   K  A  L   P  A  P  I   E  K  T
                              CH2
2021 CATCTCCAAA GCCAAAGGGC AGCCCCGAGA ACCACAGGTG TACACCCTGC
     GTAGAGGTTT CGGTTTCCCG TCGGGGCTCT TGGTGTCCAC ATGTGGGACG
365   I  S  K   A  K  G  Q   P  R  E   P  Q  V   Y  T  L  P
         CH2                     CH3
2071 CCCCATCCCG GGAAGAGATG ACCAAGAACC AGGTCAGCCT GACCTGCCTG
     GGGGTAGGGC CCTTCTCTAC TGGTTCTTGG TCCAGTCGGA CTGGACGGAC
382   P  S  R   E  E  M   T  K  N  Q   V  S  L   T  C  L
                               CH3
2121 GTCAAAGGCT TCTATCCCAG CGACATCGCC GTGGAGTGGG AGAGCAATGG
     CAGTTTCCGA AGATAGGGTC GCTGTAGCGG CACCTCACCC TCTCGTTACC
398  V  K  G  F   Y  P  S   D  I  A   V  E  W  E   S  N  G
                              CH3
2171 GCAGCCGGAG AACAACTACA AGACCACGCC TCCCGTGCTG GACTCCGACG
     CGTCGGCCTC TTGTTGATGT TCTGGTGCGG AGGGCACGAC CTGAGGCTGC
415   Q  P  E   N  N  Y  K   T  T  P   P  V  L   D  S  D  G
                              CH3
2221 GCTCCTTCTT CCTCTACAGC AAGCTCACCG TGGACAAGAG CAGGTGGCAG
     CGAGGAAGAA GGAGATGTCG TTCGAGTGGC ACCTGTTCTC GTCCACCGTC
432   S  F  F   L  Y  S   K  L  T  V   D  K  S   R  W  Q
                              CH3
2271 CAGGGGAACG TCTTCTCATG CTCCGTGATG CATGAGGCTC TGCACAACCA
     GTCCCCTTGC AGAAGAGTAC GAGGCACTAC GTACTCCGAG ACGTGTTGGT
```

Fig. 18G

```
448  Q  G  N  V   F  S  C   S  V  M   H  E  A  L   H  N  H
                              CH3
2321 CTACACGCAG AAGAGCCTCT CCCTGTCTCC GGGTAAATGA
     GATGTGCGTC TTCTCGGAGA GGGACAGAGG CCCATTTACT
465   Y  T  Q   K  S  L  S   L  S  P   G  K  O
                         CH3
```

Fig. 18H



SKMES
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
OD 540 nm
0.0001
0.001
0.01
0.1
1
10
Concentration µg/ml
F(ab)'2 4H6 + αmFc
Ch4H6 + αHFc
4H6 + αmFc
Apo2L

Fig. 19

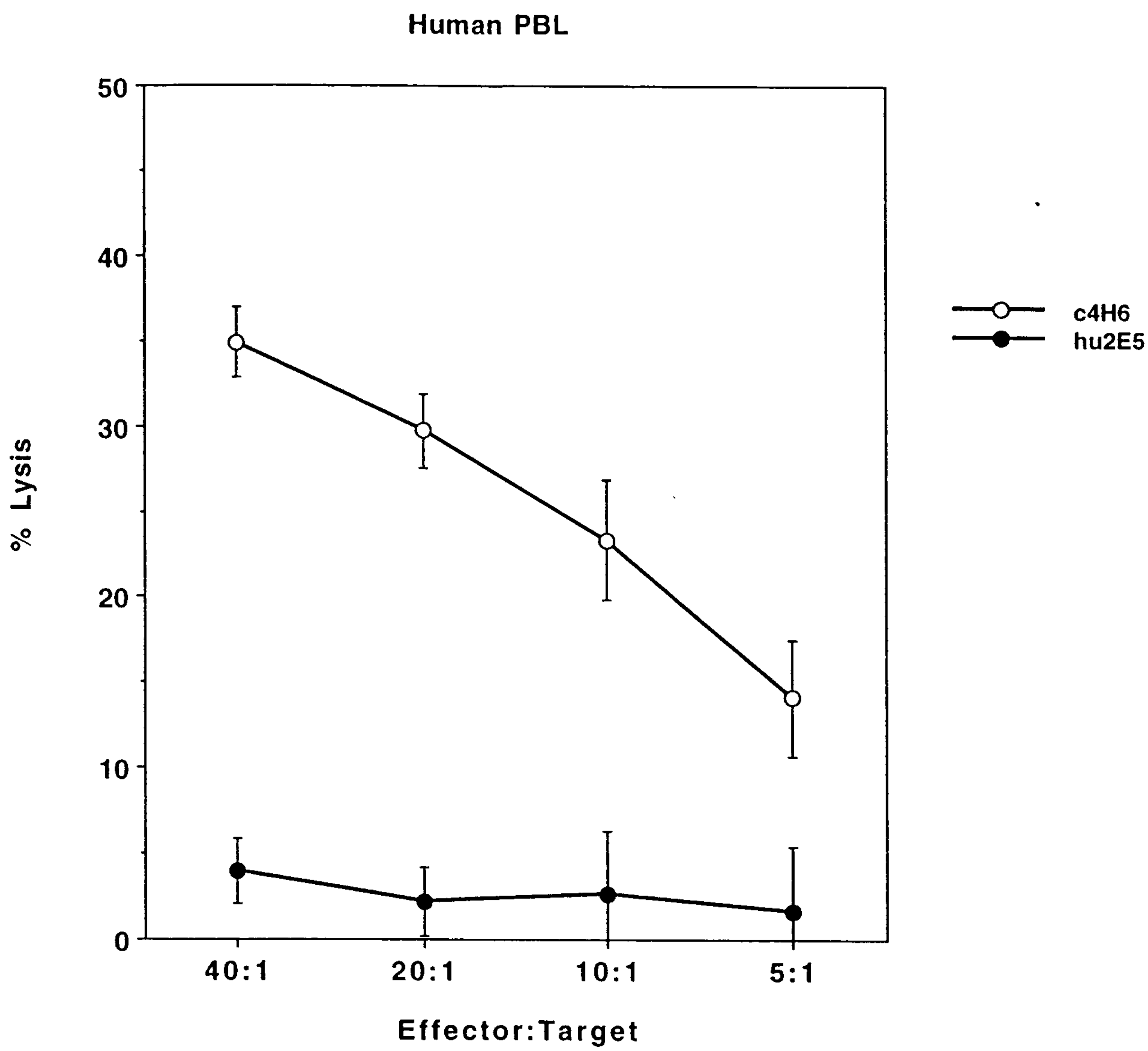

Human PBL
50
40
30
20
10
0
% Lysis
40:1
20:1
10:1
5:1
Effector:Target
c4H6
hu2E5

Fig. 20

Comparison of the in vivo efficacy
of Murine and Chimera 4H6

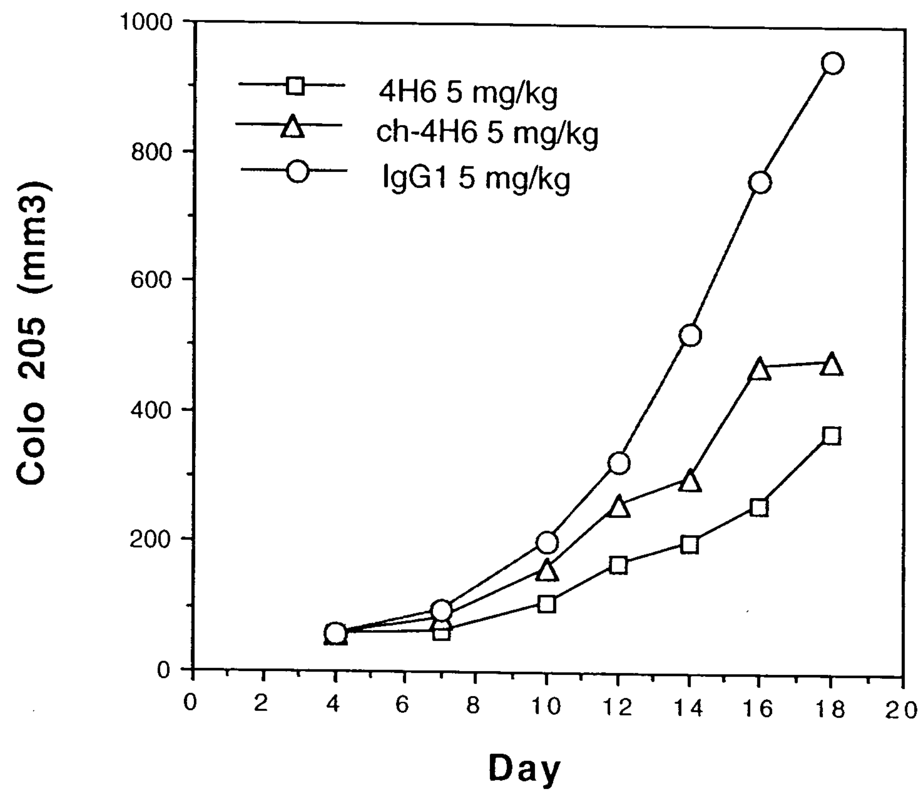


Fig. 21